REMARKS

Applicants respectfully request that prior to further substantive examination the foregoing amendments and the following remarks be made of record in the instant case.

I. Status of the Claims

Claims 14-57 are pending in the instant application and stand variously rejected under 35 U.S.C. §112, first paragraph for allegedly lacking of enablement and/or written description, under 35 U.S.C. §112, second paragraph as assertedly being indefinite for failing to particularly point out and distinctly claim the invention, and under the judicially created doctrine of obviousness-type double patenting. Applicants respectfully traverse the rejections and request reconsideration in light of the above amendments and the following remarks.

II. The objection to claim 14 as being dependent from a non-elected claim should be withdrawn

Claim 14 was objected to as being dependent from non-elected claim 3. Applicants thank the Examiner for considering claim 14 as having incorporated therein the matter of claim 3. Applicants have addressed the informality of claim 14 by presenting an amendment that incorporates all of the subject matter of claim 1 (from which claim 3 depends) into claim 14. Applicants request that the objection be withdrawn in view of this amendment.

III. Rejection under 35 U.S.C. §112, second paragraph should be withdrawn

Claims 14-28, 34, 36, 37, 38, 47, and 54-57 were rejected under 35 U.S.C. §112, second paragraph as assertedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention.

Claims 14 and 15-28 were rejected as allegedly being indefinite because it is alleged that it is unclear whether the treatment is aimed specifically at humans or all animals. Claim 29 and claims 30-38 depending therefrom, were similarly rejected. Applicants submit

that all animals that have a disease caused all or in part by a deficiency in α-L-iduronidase may be treated using the methods of the present invention. However, in order to expedite the prosecution of the claims, Applicants have amended the preamble of claim 14 and claim 29, to recite "treating human diseases caused all. . ." This amendment uses language similar to the language suggested by the Examiner at page 3 of the Office action and Applicants believe it obviates the grounds for the rejection.

Claim 34 was rejected for lacking antecedent basis for the term "to a patient suffering from a deficiency thereof." Applicants have amended the claim to recite " to said human subject wherein said human subject is suffering from a deficiency thereof." Applicant believe this amendment overcomes the rejection.

Claim 36 was rejected for lack of antecedent basis for the term "said infusion" in line 1. Applicants have amended this claim to refer to claim 35, thereby correcting the antecedent basis of the claim.

Claim 14 and dependent claims 15-28 were rejected under 35 U.S.C. §112, second paragraph, because according to the Examiner the metes and bounds of terms "efficacy endpoints" in steps (b) through (e) were not clear to the Examiner. Applicants respectfully traverse the rejection. Applicants believe that claim 14 and the claims depending therefrom to be in compliance with 35 U.S.C. §112, second paragraph. Those of skill in the art are aware of a variety of efficacy endpoints that can be used to monitor the efficacy of a given enzyme replacement therapy in the treatment of lysosomal storage disease. For example, the specification at page 37, line 20 through page 38, line 11 teaches various endpoints that are recognized in the art. Those of skill in the art of enzyme replacement therapy for lysosomal storage diseases will be aware of other efficacy endpoints that can be used instead of the specific endpoints provided in that section of the application. Given the teaching in the specification and the level of skill in the art, a skilled person is presented with, and is aware of, numerous endpoints that can be monitored. As indicated in MPEP 2173.02:

> "[d]efiniteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;
(B) The teachings of the prior art; and
(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

Applicants submit that the content of the specification provides exemplary guidance as to what each of the endpoints of (b) through (e) may be, and those of skill in the art will be aware of other such parameters that could readily substitute for these specific endpoints and would view each of steps (b) through (e) as guiding the skilled artisan to review such endpoints. As such, Applicants believe that claim term "efficacy endpoints" is sufficiently definite without unduly limiting the scope to which applicants are entitled. In light of these comments, Applicants request that the rejection be withdrawn.

Claim 15 was rejected for indefiniteness of the terms "percent predicted forced vitality capacity" and "six minute walk distance." Claim 16 was similarly rejected for reciting "liver organ volume," and "disability score index," and claim 17 was rejected for reciting "urinary glycosaminoglycan levels," "quality of life." Applicants respectfully disagree that these claims are indefinite. Claim 26 and 37 were rejected for reciting the term "reduces lysosomal storage." Claim 27 was rejected for reciting the phrase "causes improvement" and claims 28 and 38 were rejected for reciting the terms "increase" and "reduction," as these terms are considered by the Examiner to be "open" language. In each case, the Examiner requested that Applicants provide a numerical value for each parameter being monitored. Claim 57 was rejected for reciting "reduction in said tricuspid regurgitation," as this term was allegedly not clear. Applicants respectfully traverse each of these rejections. These claims all recite clinical parameters that are routinely used by those of skill in the art to monitor the efficacy of a given treatment for a lysosomal storage disease. The parameters typically are measured before and after the administration of the particular therapy, and a comparison of such "before" and "after" measurements thus reveals whether the therapy has had the desired effect. This is a qualitative determination and, need not, and should not be limited to specific numerical boundaries, as these boundaries can vary without departing from providing a clinically relevant diagnosis/prognosis. Applicants have shown

how these tests may be performed in a clinical setting in *e.g.*, a phase I study (see e.g., pages 38-41 of the specification.) Applicants submit that when the claims are reviewed in light of these teachings of the specification, as opposed to in an abstract vacuum, the claims are sufficiently definite and clear to one skilled in the art of performing diagnostic and prognostic determinations.

Applicants submit that the above amendments and comments address all of the rejections based on 35 U.S.C. §112, second paragraph and request that the rejections be withdrawn in light of these comments.

IV. Rejection under 35 U.S.C. §112, first paragraph for lack of written description should be withdrawn

Claims 14-38 and 39-57 were rejected under 35 U.S.C. §112, first paragraph for allegedly containing subject matter which was not described in such a way as to reasonably convey to one of skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Briefly reiterating the rejection, the Office Action states that "the specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ OD NO: 2" (Office action, page 11) and that the disclosure of "only a single species of the claimed genus is insufficient to put one of skill in the art in possession of the attribute and features of the all species within the claimed genus." Applicants respectfully traverse the rejection.

First and foremost, Applicants submit that each of the pending claims is drawn to a ***method*** of treatment, a patentable category of subject matter that is distinct from the category of ***compositions*** (see 35 U.S.C. §101). The Examiner appears to have overlooked this distinction in supporting the rejection of these claims for lack of written description of "all species within the claimed genus." The Federal Circuit has previously stated that the "purpose of the 'written description' requirement is . . .[to] convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now

claimed." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). Thus, the focus of a written description enquiry should be to look to ***whatever is now claimed***, with the view to showing whether the inventor had possession of the claimed subject matter. The claims in question here are claims to ***methods of treatment*** and not to protein sequences. When the query is refocused on the subject matter being claimed it becomes apparent that such subject matter is fully described by the specification in such a manner as to convey with reasonable clarity that the inventors were in possession of the invention.

It is beyond question that the specification teaches and describes methods of treating diseases caused all or in part by a deficiency in α-L-iduronidase, using a composition comprising a protein having the sequence of SEQ ID NO:2 and a purity of greater than 99%. Thus, the point of contention revolves around whether the specification shows possession of treatment methods that employ compositions comprising fragments or mutants of SEQ ID NO:2 that also possess the same or similar activity as a human α-L-iduronidase of SEQ ID NO:2. Applicants submit that the specification does provide such a teaching, and that the case-law and the United States Patent and Trademark Office Written Description Guidelines compel a finding that the claims as presented are supported by the written description found in the specification.

At page 10, lines 9 to 10, the specification expressly states that the inventors contemplate producing "α-L-iduronidase in amounts which enable ***using the enzyme therapeutically***" and that those skilled in the art should be able to "design fragments of cDNA encoding ***biologically active fragments and mutants*** of the naturally occurring α-L-iduronidase which possess the same or similar biological activity to the naturally occurring full-length enzyme" (specification page 8, lines 2-4). The full-length enzyme is expressly taught in the specification, and is known to those of skill in the art as having a sequence of SEQ ID NO:2. The specification in Examples 1 and 5-6 further proceeds to provide specific guidance to those of skill in the art how to produce α-L-iduronidase (Example 1, pages 28 to 30) for use in therapeutic methods in humans (Examples 5-6, pages 32-41). Thus, from the above, it is established that the specification contemplated methods of treatment of diseases caused all or in part by a deficiency in α-L-iduronidase, using not only the full length sequence but also biologically active fragments or mutants of such an enzyme.

Applicants submit that is inappropriate to judge the written description of the presently claimed ***methods*** based on a legal standard involving ***protein composition inventions***. As stated in the Federal Register when the Written Description Guidelines were promulgated "[t]he description need only describe in detail that which is new or not conventional." (See 66 FR 1106). This statement echoes the well established legal tenet that a disclosure need not teach, and preferably should omit, what is well known to those of skill in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). The specification has taught methods of treating diseases caused all or in part by a deficiency in α-L-iduronidase. Applicants have amended the claims to clarify that the α-L iduronidase sequence has a sequence of SEQ ID NO:2, and that the fragments and mutants of the iduronidase are fragments of SEQ ID NO:2 that possess the same or similar activity as a protein of SEQ ID NO:2. Applicants stress, however, that the present claims do not attempt to claim a genus of compounds that must be structurally distinguished from all other compounds. Instead, the present invention is directed to ***a method of using*** an iduronidase enzyme, or a fragment, or a mutant thereof, in a therapeutic method, and is based in part on the discovery that using such proteins of a purity of 99% or higher achieves beneficial therapeutic results. Thus, the methods of the instant invention represent a novel and nonobvious way to treat individuals having diseases caused all or in part by a deficiency in α-L-iduronidase, using fragments and mutants of an iduronidase enzyme of SEQ ID NO:2, and are not specifically directed or limited to the use of an iduronidase protein only having the sequence of SEQ ID NO:2.

The Federal Register in discussing the Written Description Guidelines recognized that an Applicant can show possession of the claimed invention by describing distinguishing, identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. (See 66 FR 1104, col. 3.) "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognized that the inventor had possession of the claimed invention." (66 FR 1105, col. 3.) In the case of the presently claimed methods, the distinguishing characteristic need not be structural characteristics of compounds (*i.e.*, the protein sequence), but rather the steps of the methods of using enzymes of a given purity level (See 66 FR 1106, cols. 1-2, distinguishing structures

of products from steps of a process.) Since the present claims are directed to such methods, Applicants submit that the specification reasonably conveys the invention to persons of ordinary skill and is reasonably commensurate in scope with the teachings of the invention. These claims will not "encompass" compounds, but rather describe a particular method for using enzymes in the treatment of diseases caused all or in part by a deficiency in α-L-iduronidase, and this use represents one of the Applicant's contributions to this field.

Moreover, contrary to the Examiner's assertions, the claims do not recite methods of using "unrelated" compounds. As mentioned above the amended, independent claims 14, 29, 34, 36, and 39 all recite a sequence, and these claims also all recite specific activities that are associated with the activity of the iduronidase.

Finally, also indicative of the fact that the instant claims meet the written description requirement is the fact that the instant claims are akin to the claim set forth in Example 18 of the Revised Interim Written Description Guidelines found at www.uspto.gov/web/menu/written.pdf, which provides guidance to Applicants and Examiners alike as to how to approach a "process claim where the novelty is in the method steps."

In Example 18 of the above-referenced Guidelines, the specification was found to have taught a method for producing proteins from *Neurospora crassa*. In the method, mitochondria were isolated from this fungus and transformed with a mitochondrial expression vector which comprises a nucleic acid encoding a protein of interest. The protein was subsequently expressed and isolated from the mitochondria. The specification exemplified the expression of α-galactosidase by the claimed method using a cytochrome oxidase promoter. The claim in question read:

> "A method of producing a protein of interest comprising;
> obtaining Neurospora crassa mitochondria,
> transforming said mitochondria with a expression vector comprising a nucleic acid that encodes said protein of interest,
> expressing said protein in said mitochondria, and
> recovering said protein of interest."

In analyzing the claim, the Guidelines recognized that the sequence of the nucleic acid is not essential to the claimed invention and a search of the prior art revealed that the claimed method of expression in *Neurospora crassa* is novel and unobvious. ***That is exactly the situation presented here.*** To the knowledge of the Applicants, there is no prior art that teaches treatment methods for diseases caused all or in part by a deficiency in α-L-iduronidase using such a protein with a greater than 99% purity. Indeed, it appears that no such art is within the knowledge of the United States Patent and Trademark Office either, because none has been cited.

Next, the Guidelines explained in Example 18, that the claim was drawn to a genus, *i.e.*, any of a variety of methods that can be used for expressing protein in the mitochondria and there was an actual reduction to practice of a single embodiment, *i.e.*, the expression of α-galactosidase. Likewise, the claims of the instant invention may be drawn to a genus of treatment methods which employ variants of a protein of SEQ ID NO:2, which variants may be fragments or mutants, but all of which possess a biological activity the same as or similar to that of SEQ ID NO:2. As with Example 18, there are a limited number of ways of practicing the process steps of the presently claimed treatment methods. And the embodiments of the treatment methods using a protein of SEQ ID NO:2 having a purity of 99% or greater are representative of the genus based on the disclosure of those methods, considered along with the level of skill and knowledge in the gene expression art. One of skill in the art would recognize that Applicant was in possession of all of the various expression methods necessary to practice the claimed invention. Therefore, if the claims of the present invention are analyzed as method claims, and are reviewed in view of the guidance presented in the Revised Written Description Guidelines, Applicants submit that the claimed invention is adequately described.

In view of the above discussion, Applicants respectfully submit that the rejection of claims under 35 U.S.C. §112, first paragraph for lack of written description is overcome and that the rejection should be withdrawn. Applicants respectfully request such favorable reconsideration of claims 14-57.

V. Rejection under 35 U.S.C. §112, first paragraph for lack of enablement should be withdrawn

Claims 14-57 were rejected under 35 U.S.C. §112, first paragraph for lack of enablement for a method of treatment using greater than 99% pure, fragments or muteins of a recombinant α-L iduronidase enzyme that has a sequence of SEQ ID NO:2. Applicants respectfully disagree with the Examiner and traverse the rejection.

The claims of the present application are directed to methods of treating diseases caused all or in part by a deficiency in α-L-iduronidase, by administering compositions that comprise α-L iduronidase enzyme. As amended herein above the claims defined the α-L iduronidase enzyme as having a sequence of:

> "SEQ ID NO:2, or biologically active fragment of SEQ ID NO:2 which possesses the same or similar biological activity to SEQ ID NO:2 or a mutant of SEQ ID NO:2 which possesses the same or similar biological activity to SEQ ID NO:2, wherein said human recombinant α-L-iduronidase of SEQ ID NO:2, biologically active fragment or mutant thereof has a purity of greater than about 99%. (see *e.g.*, claim 14)

The Examiner acknowledges that the specification provides enablement for a for a method of treatment using greater than 99% pure, recombinant α-L iduronidase enzyme with a sequence of SEQ ID NO:2. As discussed below, Applicants submit that given the disclosure of the instant specification, those of skill in the art would be able to prepare and use fragments and mutants of a protein of SEQ ID NO:2 in the treatment methods in much the same manner as preparing proteins of a sequence of SEQ ID NO:2 without undue experimentation, and as such, the Applicants have fully enabled the scope of the methods claimed herein.

In supporting the rejection, the Examiner suggested that factors to be considered in determining whether undue experimentation would be required are those that were summarized in *In re Wands* 858 F.2d 731, 8 USPQ 2d 1400 (Fed Cir. 1988).

Applicants agree with the Examiner that the factors of *In re Wands* should be used to determine whether the specification provides enablement commensurate with the scope of the claims. However, Applicants submit that the claims of the present application are in full compliance with the edicts of *In re Wands*. Applying the standards summarized in *Wands*, the present specification does indeed provide a reasonable amount of guidance to one of skill in the art.

The methods of the present invention are designed to overcome a problem in the art, which relates to the fact that in the prior art treatment methods used iduronidase compositions of "degrees of purity between 90% and less than 99%, which is not optimal for long-term human administration (See FIG. 12)" and that "[t]reatment with human recombinant α-L-iduronidase with a minimum purity of 97% was associated with some clinical reactions, specifically hives in 5 patients, and complement activation in 4 patients." The specification expressly guides that the problem being solved by the instant invention stems from the fact in the prior art treatment methods there is "a reaction to a protein that is a trace contaminant to the α-L-iduronidase. (FIGURE 2)" (specification page 22, lines 26-27) and that "a greater than 97% purity is adequate for patient use, higher levels of purity are desirable and preferable." (see specification page 23, lines 7-9).

To alleviate the above-identified problem, the specification teaches that one of skill should produce greater than 97% purity and show that "[a]s shown in FIG. 12, the optimized purification scheme described above achieves a degree of purity that is greater than 99% and importantly reduces Chinese hamster ovary cell host proteins to less than 1 percent, as determined by the Chinese Hamster Ovary Protein (CHOP) assay." The specification uses wild-type α-L-iduronidase as an example of one such purified enzyme composition, but those of skill in the art will recognize that it will be possible to make other iduronidase compositions which could be used in the treatment methods. The sequence of human α-L-iduronidase was known to those of skill in the art prior to the filing date of the present application. Methods and compositions for making recombinant proteins that are fragments or mutants of SEQ ID NO:2 in *e.g.*, CHO cells are well known to those of skill in the art and could be made in much the same manner as described for recombinant expression of a protein of SEQ ID NO:2 in Example 1 at pages 28-30 of the specification. Having made the

recombinant protein, one skill in the art need only follow the teachings of the specification (*e.g.*, as outlined in FIG. 2), to purify the proteins. Use of such purified protein fragments or mutants of SEQ ID NO:2 in the treatment of diseases caused all or in part by a deficiency in α-L-iduronidase would be the same as the use of compositions that comprise a protein of the sequence of SEQ ID NO:2. Given that all of these teachings are expressly detailed in the specification, it is beyond question that the claims of the present invention are fully enabled.

Performing the methods of the invention will require ***only some routine*** experimentation. As the court in *In re Wands* instructed "[e]nablement is not precluded by the necessity for some experimentation." Indeed, it is inevitable that there may be some quantity of experimentation required. Nonetheless, the key word is ***undue***, and not experimentation. *In re Wands*, 8 USPQ2d 1400, 1404. The court went on to state that a considerable amount of experimentation is, in fact, permissible if it is merely routine ***or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*** *Id.* Applicants submit that the working examples of the specification and the guidance that an iduronidase composition having a purity level of 99% or greater and having less than 1% contaminants from the production method have beneficial therapeutic effects can be used provide a sufficient and reasonable amount of guidance as to the direction in which the skilled artisan should proceed to produce mutants and fragments of iduronidase to produce additional effective therapeutic human α-L-iduronidase compositions. Therefore, the first and second *Wands* criteria quoted by the Examiner at page 8 of the Office action (*i.e.*, (1) that the quantity of experimentation not be undue and (2) the presence of guidance/direction in the specification) are met.

In addition, the specification provide explicit working examples of the methods being claimed in the instant application, thereby meeting a third *Wands* factor that suggests that the specification is enabling for the claimed invention, if a working examples are provided therein (listed as requirement (3) by the Examiner at page 8 of the Office action). In the working examples, the inventors show how to produce highly purified recombinant α-L-iduronidase (See Example 1) and how to treat dogs and cats (See Example 4) and humans (Examples 5 and 6) with highly purified recombinant human α-L-iduronidase

and show that use of such highly purified compositions results in clinical and biochemical improvement in patients with Mucopolysaccharidosis I.

Given the express working examples in the specification, one of skill in the art could readily use information readily available in the art (*i.e.*, the protein and nucleic acid sequence of wild-type human α-L-iduronidase) to produce fragments and mutants of the protein and use those fragments and mutants in the methods of the present invention in the treatment of diseases caused all or in part by a deficiency in α-L-iduronidase.

Moreover, while it is true that not all of the factors need to be addressed, the remaining *Wands* factors argue in favor of enablement. For instance, 4) the nature of the claimed invention is one in which 5) the level of skill of the ordinary artisan is high. The field of the invention is in the area of therapeutic intervention of lysosomal storage diseases using enzyme replacement therapy. This general field has been known and investigated for a number of years (see background of specification). It was determined based on animal models of MPS I that diseases, such as mucopolysaccharidosis I, which are caused all or in part by a deficiency in alpha-L-iduronidase, may be treated by administering enzyme replacement therapy. However, prior to the present invention, the enzyme replacement therapy was not effective for long-term human treatment because the prior art employed compositions that were contaminated with more than 1% contaminants from the production process. The recognition that shifting from a 97% level of purity of enzyme to a 99% purity of enzyme produced a long-term therapeutically beneficial effect was presented for the first time by the inventors in the present specification. Thus, the state of the prior art (criterion (5) listed by the Examiner on page 8 of the Office action) was that sequences of iduronidase were known, the use of this protein in enzyme replacement therapy was known, techniques for transforming cells to produce recombinant protein also were known, but the use of such 99% pure protein was not known, appreciated or contemplated by the prior art.

In addition, the relative level of skill of those in the art in the area of transforming mammalian cells with nucleic acid expression constructs is high (criterion 6 listed by the Examiner at page 4 of the Office action). Those individuals need only follow

the teachings of the instant specification and routine laboratory techniques, such as those that are presented in *e.g.*, Maniatis T, Fritsch E F, Sambrook J (1982) Molecular cloning: A laboratory manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y, to produce mutants or fragments of proteins of SEQ ID NO:2 as directed in the present invention. Therefore, the level of skill in this art is advanced.

As discussed above, the specification teaches how to successfully produce therapeutic compositions of human α-L-iduronidase. Given that one of skill in the art knew of cDNA sequence that encodes α-L-iduronidase and the level of skill in the field of transforming mammalian cells with expression vectors is high, Applicants submit that there is a sufficiently high degree of predictability in the art (criterion 7 listed by the Examiner at page 4 of the Office action) of producing mutants or fragments of SEQ ID NO:2 because recombinant techniques for making such compositions were common-place and routine at the time the instant application was filed. One of skill could readily test the mutants and fragments using any model system for mucopolysaccharidosis. Indeed, the skill artisan need look no further than the exemplary canine and feline model systems specifically identified in Example 3 (specification pages 30-31), and the protocol outlined therein to test any such fragments or mutants generated and purified using the methods of the present invention. Such testing is exactly the type of experimentation that the court in *Wands* considered to be routine, because the skilled artisan need only follow the explicit instructions laid out in the specification in order to conduct the methods of the invention.

Furthermore, the breadth of the claims is fully commensurate in scope with the teachings provided in the specification. The claims are directed to human α-L-iduronidase enzymes that have the sequence of SEQ ID NO:2, or are fragments or mutants of SEQ ID NO:2 that possess a biological activity the same as or similar to a protein having the sequence of SEQ ID NO:2 , and not to other unrelated sequences. Use of compositions comprising a protein of SEQ ID NO:2 having the specified purity have been specifically taught and the specification provides explicit instructions that one skilled in the art should produce related fragments and mutants for use in the treatment methods. The Examiner has provided no objective evidence to show that fragments or mutants of SEQ ID NO:2 would not produce the

desired therapeutic outcome or that one of skill would not be able to make and test such fragments and mutants in the assays described in the specification.

Therefore, Applicants have enabled the full scope of their claimed invention and, as the courts have indicated the '[i]nventor should be allowed to dominate . . . others . . . based in some way on his teachings, since some improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work." (*In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). This guidance from the court suggests that the present claims are not overly broad in view of the teachings of the specification and the inventors should be allowed to dominate others with the claims that cover methods of treating diseases using compositions that comprise mutants and fragments of human α-L-iduronidase of SEQ ID NO:2 that have a biological activity the same as or similar to SEQ ID NO:2 and have a purity of 99% or greater.

The above discussion of each of the *Wands* factors as applied to the claims of the present application shows that the claimed methods of the present invention are adequately and objectively enabled, by the specification as filed. As such, the Applicants respectfully request withdrawal of the rejection under §112, first paragraph, and reconsideration of the claims for allowance.

VI. Double Patenting Rejection.

Claims 14-57 were rejected under the doctrine of obviousness-type double patenting as being unpatentable over claims 1-30 of U.S. Patent No. 6,585,971. It is the Examiner's position that the since both the instant application and the claims of the 6,585,971 are directed to methods of treating using α-L-iduronidase, the claims of the instant application may not be considered patentably distinct over each other.

Without acquiescing to the Examiner's arguments, Applicants respectfully request that the Examiner hold this rejection in abeyance until such a time as when allowable subject matter is indicated in the instant case. At that point, Applicants would like the opportunity to revisit the matter and provide appropriate response with appropriate arguments

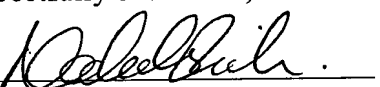
and/or a terminal disclaimer. The Examiner's discretion in this matter is respectfully solicited. In the event that the Examiner wishes to discuss this point further, Applicants respectfully invite the Examiner to contact the undersigned representative.

VII. Conclusions

Applicants believe that all of the rejections have been overcome and the claims of the instant application are now in condition for allowance and request an early indication of such a favorable disposition of the case. The Examiner is invited to contact the undersigned with any questions, comments or suggestions relating to the referenced patent application.

Dated: September 23, 2003

Respectfully submitted,

By 

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